

Chapter 5

Reproductive Effects

5.1 Introduction

The study of reproductive toxicity includes measures of: female fertility and fecundability; other female reproductive effects, such as lowered age at menopause and menstrual disorders; and male reproductive effects, including altered sperm parameters, which may influence a couple's fertility and/or fecundability. Very few studies have investigated the effects of ETS exposure on male and female reproductive function (Tables 5A and 5B). Of these, most have examined delay to conception in women who eventually achieve pregnancy, as an indication of sub-fecundability. Many of these studies were designed to look at the woman's active smoking, not ETS exposure, but also reported the husband's smoking status, a surrogate for ETS exposure used in studies of other outcomes. Three of the studies reviewed examined the possibility of an effect on women's fertility occurring earlier in development by trying to ascertain childhood and *in utero* exposure to ETS.

The discussion below of the potential impact of ETS on each outcome begins with a brief review of epidemiological studies that assessed the effect of active smoking. Although reviewing active smoking effects is not the purpose of this document, the review of these studies to provide a context within which to consider the results of the studies of ETS exposure. Epidemiologic studies of ETS exposure are discussed in more detail, followed by a description of pertinent animal studies. Studies are then discussed as a group and conclusions are presented.

5.2 Female Fertility and Fecundability

In epidemiological studies, measurement of female fertility (ability to reproduce) and fecundability (the probability of conceiving in a given menstrual cycle) generally relies on reported failure to conceive or delay to conception following a time period of unprotected sexual intercourse. Infertility is commonly defined as not becoming pregnant within a year of unprotected intercourse; of course, some couples may go on to conceive later. Fecundability may be measured by determining the number of cycles needed to conceive and calculating the conception rate in each cycle. The probabilities (or rates) of conception can then be compared between two groups – exposed and unexposed – in the form of a ratio. When such a “fecundability ratio” (FR) is less than one, it indicates that the exposed group has lower or “sub”-fecundability than the comparison group. When examining fertility and fecundability, covariates related to sexual practices are important to consider, including frequency of coitus, contraceptive use, and history of sexually transmitted diseases, as well as maternal age, socioeconomic status and reproductive history. In animal studies, measures of female fertility derived from the standard multigeneration study in rodents are the fertility index, the fecundity index, the mating index and the parturition index; however, multigeneration studies have not been conducted with tobacco smoke. Reproductive organ weights and histology, ovulation,

estrus cycles, mating behavior, implantation and resorption may be directly determined from other study designs, and effects on these parameters are considered relevant to female fertility.

5.2.1 Overview of Human Studies of Female Fertility and Fecundability and Active Smoking

Active smoking by women has been found to be associated with decreased fertility in a number of studies (reviewed in Stillman *et al.*, 1986; Westhoff, 1990; and Spira *et al.*, 1987). Associations have been found between smoking and both delay to conception and infertility, particularly related to tubal factors. Delay to conception has been measured in different time intervals, but studies have found increased risks of 40-80 percent among smokers (*e.g.*, odds ratios of 1.4-1.8) (Howe *et al.*, 1985). The studies which found an association with tubal infertility reported odds ratios of 1.6-3.3 (Daling *et al.*, 1986; Stillman *et al.*, 1986). Many of the studies have found a dose-response effect. The 1980 Surgeon General's report (U.S. DHHS, 1980) stated that "cigarette smoking appears to exert an adverse effect on fertility" and many of the important studies were conducted since that report was published. In the ETS studies reviewed below, associations reported for active smoking and fertility are presented along with the ETS findings.

5.2.2 Human Studies of Female Fertility and Fecundability and ETS Exposure

The human studies are presented below in two groups, based on when exposure to ETS occurred: first, studies are described in which exposure occurred during adulthood, usually from a smoking spouse (Table 5.1); second, studies are described in which exposure occurred during childhood from smoking parents (as well as *in utero*, or exposure as a fetus, due to maternal active smoking) (Table 5.2).

5.2.2.1 Exposure During Adulthood

Tokuhata (1968)

In the single study of infertility conducted to date, Tokuhata (1968) obtained information from the next-of-kin of 1095 cancer cases and 921 controls about the lifetime reproductive history and smoking history of the subjects and their spouses. Infertility was defined as never having been pregnant. We calculated the crude odds ratio of fertility among couples in which the wife did not smoke and the husband did smoke as 0.67 (Table 5.1). There did appear to be an association with the wife's active smoking (OR=1.5), which was diminished when only couples with nonsmoking husbands were examined (OR=1.3).

This study has a number of problems. Many of the couples (about 400) were excluded because of lack of data on husband's smoking status. The reporting by next-of-kin about pregnancies that ended in fetal loss is probably not accurate, so some women may be misclassified as infertile. There was no information available on any confounders, nor on contraceptive practices. Neither was there any detailed information on exposure to tobacco smoke during specific reproductive periods.

Baird and Wilcox (1985)

Baird and Wilcox (1985) conducted a study in Minnesota to investigate the effect of smoking on fertility. Reduced fertility was determined retrospectively as time to conception in 678 pregnant women who had stopped using birth control in order to become pregnant and who had subsequently conceived within two years. A strength of the study is that the authors made some attempt to exclude cycles "not at risk" for conception, *e.g.*, those during which women reported being sexually abstinent or using birth control. The authors found that women who were smokers had reduced fertility, with a dose-response effect. They stated that husband's smoking status did not affect fertility after adjusting for the woman's smoking status and other potential risk factors ($p=0.95$). However, no data were presented. These results may not be generalizable because the study was conducted in a population of volunteers from a group with high socioeconomic status, who had planned their pregnancies.

Suonio et al. (1990)

A study in Finland (Suonio *et al.*, 1990) examined data from interviews conducted with 2,198 women during their 20th week of pregnancy. Fecundability, or specifically, delay to conception, was analyzed by husband's smoking status. Limiting the analysis to women who conceived within 12 months, the risk of not conceiving by 6 months was 1.3 (95% CI=1.2 - 1.4) if the husband smoked and 1.5 (95% CI=1.3 - 1.8) if the pregnant woman herself smoked. Both effects were potentiated by increasing age. This effect was not seen when the entire dataset was analyzed (*i.e.*, not truncated at 12 months). The odds ratios were adjusted for some factors, but many that are related to time to conception were not available, including contraceptive practices and coital frequency. This study also did not appear to have data for determining cycles at risk of pregnancy and may thus have some misclassification bias. Furthermore, the association was examined in all pregnancies, including those of women who were active smokers as well as those of nonsmokers, and it is not clear whether maternal and paternal smoking were entered in the regression models simultaneously. If not, the results are not adjusted for smoking by the partner.

Olsen (1991)

Olsen (1991) examined fecundability in a large study of almost 11,000 Danish women who completed a questionnaire in their last month of pregnancy. The question about time to conception was pre-coded with broad categories of 0-6 months, 7-12 and greater than 12 months. Women treated for infertility were excluded. Current smoking by the woman's partner was associated with a delay to conception in the pregnancies of both smoking and nonsmoking women; a dose-response effect was more apparent in pregnancies of women who were smokers. Among nonsmoking women, the adjusted risk of not conceiving within 6 months was 1.1 if their partner smoked 1-9 cigarettes per day, and 1.3 for those whose partner smoked ten or more per day (10-19 cigarettes/day, 95% CI=1.1 - 1.6; ≥ 20 cigarettes/day, 95% CI=0.96 - 1.8). The risk for not conceiving within 12 months for these nonsmoking women with spouses who smoked was also elevated, but did not show any dose-response effect. Contraceptive practices and coital frequency

were not assessed. This analysis included women who became pregnant while using contraception, but Olsen stated that excluding these women did not change the results. The measurement of time to conception was rather crude in this study.

Florack et al. (1994)

A recent study examined cigarette smoking, alcohol consumption and caffeine intake of both partners in relation to time to conception in Dutch non-medical hospital workers. Current habits were recorded and rates of conception were followed for the next twelve months to estimate fecundability ratios. A major problem with the approach used by these investigators is that over half the study population had been trying to conceive for greater than one year prior to the beginning of the study. Not taking this attempt time into account can bias results, particularly if those having difficulty conceiving had changed habits such as smoking. The univariate analysis by proportionate hazard models showed slightly increased fecundability if either partner smoked moderately (Table 5.1). Heavier smoking by spouses made no difference in time to conception, while heavier smoking by females was associated with a slight decrement in fecundability. No data on per-cycle conception rates were reported. Adjusted odds ratios were not presented, although they were reported to change little. No data on confounders such as frequency or timing of intercourse were available. The association of fecundability with spousal smoking was not examined separately for female nonsmokers, so the possible effects of ETS exposure cannot be estimated.

5.2.2.2 Exposure *In Utero* or During Childhood

Wilcox et al. (1989)

In the Wilcox *et al.* (1989) study, women who participated in the Minnesota study described above (Baird and Wilcox, 1985) were re-interviewed about the smoking status of their mother when she was pregnant with them, as well as about household smokers during their childhood. The authors found that women exposed to ETS as children became pregnant faster than unexposed women. In other words, their probability of conceiving in a given menstrual cycle (fecundability) was higher than in the unexposed women. This association was present irrespective of who the household smoker was, and was slightly stronger with more smokers in the household. The adjusted fecundability ratio (FR) was 1.3 for one or two household smokers and 1.4 for more smokers. Controlling for exposure due to the woman's mother smoking during pregnancy (*in utero* exposure) in the regression model made these associations slightly stronger, with an FR of 1.6 (95% CI=1.1 - 2.2) for three or more household smokers. *In utero* exposure to maternal smoking showed a weak association with reduced fecundability (FR = 0.9, 95% CI=0.7 - 1.1). Women who were exposed to tobacco smoke during childhood but not *in utero* had an FR of 2.0 (95% CI=1.3 - 2.9) compared to unexposed women. Age at menarche was not altered by ETS exposure in childhood. Several co-variables that may confound the association were not controlled, particularly socioeconomic variables relating to the women's parents. The authors speculated on possible biological mechanisms to explain this unexpected finding, including earlier maturation and

accelerated growth of oocytes in exposed females, or induction of liver enzymes in ways that change adult patterns of hormone metabolism.

Weinberg et al. (1989)

The second study with data on the issue of fecundability and childhood ETS exposure was conducted in North Carolina to examine rates of very early fetal loss (Weinberg *et al.*, 1989). The study participants (n=230), who were enrolled at the time they discontinued contraception, collected urine for six months and were then re-contacted at 12 and 24 months if they had not yet conceived. Time to conception was truncated at 13 months so that treatment for infertility would not effect the analysis.

According to the authors, when adjustment was made for *in utero* tobacco smoke exposure and other variables (*e.g.*, age, frequency of intercourse, age at menarche and current smoking status) in a proportional hazards model, there was an association of childhood exposure with increased fecundability; without adjustment, there was no association. The adjusted FR was 1.3 (95% CI=0.9 - 1.8) for one household smoker and 1.6 (95% CI=1.0 - 2.4) for two smokers. The authors also reported that *in utero* exposure reduced fecundability (adjusted FR=0.5, 95% CI=0.4 - 0.8). This study did not consider the spouse's smoking status, or other sources of ETS exposure in adulthood. These results support the findings of the Minnesota study with respect to childhood exposure, but indicate a much stronger association of reduced fecundability with *in utero* exposure. The authors concentrated their discussion on this reduced fecundability and did not comment on the childhood ETS findings. No other information about the mothers of these women was available for analysis.

Schwingl (1992)

A recent study available as a dissertation (Schwingl, 1992) was conducted in association with researchers Baird and Weinberg, who conducted studies described above. In this study, daughters of women who had participated in the Child Health and Human Development studies of the 1960's were followed into adolescence and recontacted when they were of reproductive age. Thus, prospectively collected data were available on prenatal (or *in utero*) exposure of women who were now approximately 30 years old. These women completed questionnaires about their most recent non-contracepting interval (NCI) (of sexual activity) to determine "attempt" times or time to conception. Women never at risk of pregnancy were excluded, but unlike the two previous studies, not all NCIs ended in pregnancy. The crude FR for *in utero* smoke exposure varied only slightly with adjustment for various confounders, and the final model yielded a FR of 1.2 (95% CI =0.9 - 1.4). Adding childhood exposure to the model reduced the *in utero* FR slightly to 1.1. Childhood ETS exposure (one or two parents smoking) was associated with FRs of 1.1-1.2. Current smoking by the daughters was also not associated with fecundability (FR = 1.0-1.1 by amount smoked).

These findings do not support the findings of the two earlier studies with respect to increased fecundability among women exposed to ETS as children. The finding of little association with *in utero* smoke exposure is similar to the Wilcox *et al.* (1989) study, but

not that of Weinberg *et al.* (1989). The finding of no association of reduced fecundability with active smoking is inconsistent with most of the studies discussed above and in the literature. The sample for this study was highly selected as it included only women who had remained in a longitudinal study during their childhoods and who were still traceable; these women tended to come from families of higher socioeconomic status than the original study population and were mostly white. However, the mothers of the sample women had smoking habits very similar to those of the original study population.

5.2.3 Animal Studies of Female Fertility and Fecundability and Tobacco Smoke Exposure

The standard study design for evaluating male and female reproductive toxicity, the multi-generation breeding study, has apparently not been conducted with tobacco smoke. One abstract using such a design was located (Mays *et al.*, 1987), but a report of the full study was not found in the literature.

Two studies of ovarian cyclicity in female rats using mainstream smoke have been reported. Tachi and Aoyama (1983, 1988a) found disrupted estrus cycles but no effect on ovulation (number of corpora lutea produced once estrus occurred) or mating behavior (once estrus occurred) with inhalation exposure to mainstream smoke. McLean *et al.* (1977) found that mainstream smoke exposure in rats delayed the luteinizing hormone surge associated with ovulation. In this study, the incidence of ovulation was reduced in rats exposed to smoke from a high (but not a low) nicotine cigarette. No studies of ovarian cyclicity using sidestream smoke have been reported.

An early study described ovarian atrophy in young mice after 2-3 months of exposure to mainstream smoke (Essenberg *et al.*, 1951). A study demonstrating oocyte destruction after exposure to cigarette condensates has also been conducted (Mattison *et al.*, 1989), but a full report of these data was not located in the literature. No studies of ovarian pathology using sidestream smoke were located.

Studies using sidestream smoke exposure during pregnancy (discussed in Section 3.2.3) also contain information on female reproductive toxicity, such as implantation and resorption rates and litter size. Of the three studies using sidestream smoke, one (Witschi *et al.*, 1994) reported a reduced number of uterine implantation sites and a smaller number of live pups at the end of gestation in rats, while the other two (Leichter, 1989; Rajini *et al.*, 1994) did not. The discrepancy between the Witschi *et al.* study and the Rajini *et al.* studies, which used identical sidestream smoke exposure methodology, may be due to the timing of the exposures. In the Rajini *et al.* study, rats were not exposed on gestation days 4 and 5, the days immediately preceding implantation (on day 6), while Witschi *et al.* exposed their animals continuously from days 3 through 10 gestation.

5.2.4 Discussion and Conclusions

By its association with various adverse reproductive outcomes as well as certain chronic diseases, cigarette smoking appears to be anti-estrogenic (Baron *et al.*, 1990). Several studies have reported finding altered levels of hormones or their metabolites in smokers

compared to nonsmokers. Both the steroids, estrogen and progesterone, as well as homeostatic hormones (from the adrenal or pituitary glands) may be affected (MacMahon *et al.*, 1982; Michnovicz *et al.*, 1986; Seyler *et al.*, 1986; Barrett-Connor, 1990; Canick and Barbieri 1990; Stillman *et al.*, 1986). Nicotine has been suggested as the primary constituent in tobacco smoke that produces these effects (Stillman *et al.*, 1986).

The study of infertility (and fecundability) is complicated by the fact that it includes a number of components that may have different causes. Successful reproduction is a multi-step process that includes gametogenesis, ovulation, fertilization, tubal transport, implantation and early placentation, any of which might be affected by tobacco smoke exposure. The entire process is mediated by hormones, so an alteration in their production or metabolism caused by constituents of tobacco smoke could impair fertility. The processes most affected by such alterations would likely be ovulation and perhaps implantation.

Other mechanisms have been suggested to explain an association between smoking and reduced fertility (Stillman *et al.*, 1986). Some human and animal studies have suggested an effect of tobacco smoke or nicotine on tubal physiologic features leading to altered tubal transport, which supports the findings of an association of smoking with tubal infertility. Animal data suggest that exposure to tobacco smoke, or its constituents nicotine and PAHs, results in oocyte/follicle destruction, which could lead to reduced fertility.

In summary, the mechanism by which smoking may affect fertility has not been definitively identified, but such an effect appears plausible; the epidemiologic literature on active smoking and fertility is supportive of an effect. If active smoking leads to reduced fertility, ETS exposure might also be associated with reduced fertility. The epidemiologic data on this topic are not extensive and show mixed results. Three studies examined conception delays (in women who ultimately became pregnant) with respect to spousal smoking habits. Two of the studies (Suonio *et al.*, 1990; Olsen 1991), both conducted in Scandinavia, found slightly (about 30%) but significantly increased risks of conception delays (of six to twelve months). This is only slightly lower than the magnitude of association seen with active smoking. A study in the United States did not find such an association (Baird and Wilcox, 1985), nor did a study of time to conception in Dutch women (Florack *et al.*, 1994). With the data provided it is not possible to compare the different studies in terms of smoking rates or proportions of conceptions delayed, but exposures may well be more intense in Scandinavia where smoking is generally more accepted and prevalent. On the other hand, the U.S. study had more information about sexual practices and evaluated delay to conception in a more rigorous fashion than did either of the "positive" Scandinavian studies. In addition, because ETS exposure is defined as spousal smoking in these studies, the association seen may be due to direct effects on male reproductive parameters. Thus, it is not possible to determine from the studies conducted to date whether ETS exposure as an adult is associated with female fertility.

Three studies examined childhood ETS exposure and fecundability (Wilcox *et al.*, 1989; Weinberg *et al.*, 1989; Schwingl, 1992). Two of them, conducted by the same investigators but in different populations, found that childhood exposure tended to increase the fecundability ratio, or likelihood of conceiving; the third study did not confirm this finding. Potential problems with the studies of childhood exposure include the reliability of exposures reported with a longer period of recall and the lack of ascertainment of other covariates associated with childhood exposure. No mechanism to explain this increased fecundability has been suggested by the data collected to date. An inconsistency in these data is that *in utero* exposure to tobacco smoke (from maternal active smoking) was not associated with a similar pattern of increased fecundability. Such exposure occurs at another time in development (and is not considered to be ETS exposure for the purpose of examining reproductive and developmental effects in this document).

Animal studies have demonstrated effects of tobacco smoke exposure on ovarian cycles and implantation that are compatible with reduced fertility. However, multigeneration studies, which would provide a more complete evaluation of effects of chronic exposure on production of offspring, have not been conducted.

In conclusion, the data are inadequate to determine whether there is an association of ETS exposure with effects on fertility or fecundability.

5.3 Other Female Reproductive Effects

In addition to studies of fertility and fecundability, investigators have examined the role of exposure to tobacco smoke on earlier age at menopause and on rates of menstrual disorders.

5.3.1 Overview of Human Studies of Other Female Reproductive Effects and Active Smoking

Substantial data exist to document that smokers have earlier age at menopause (U.S. DHHS, 1980; Midgette and Baron, 1990; Tajtakova *et al.*, 1990). The mean age at menopause in smokers is on average two years less than that of nonsmokers. Some studies have also suggested increases in menstrual disorders associated with cigarette smoking (Brown *et al.*, 1988; Sloss and Frerichs, 1983). Furthermore, as discussed above (Section 5.2.4), cigarette smoke appears to be anti-estrogenic and may affect homeostatic hormones as well.

5.3.2 Human Studies of Other Female Reproductive Effects and ETS Exposure

Everson et al. (1986)

Everson *et al.* (1986) reported an association of ETS exposure and lower age at menopause. Data were obtained from 261 women who had been controls in a case-control study of cancer in North Carolina. The mean age at menopause was reduced by two years among nonsmoking women whose spouses smoked, compared to those whose

spouses did not smoke. The risk of early menopause was elevated in nonsmokers exposed to ETS ("passive smokers") compared to those not exposed (OR=1.9, 95% CI=1.0 - 3.9). Adjustment for some confounders (age, race, education and alcohol intake) increased the odds ratio to 2.1 (95% CI=1.0 - 4.5). Both these measures were similar to the association observed for active smoking and earlier age at menopause in this study. The authors found that childhood exposure to paternal smoking was not associated with early menopause. Only four subjects had mothers who smoked and these subjects' age at menopause was reduced about two years. These findings were reported in a brief format, so details of the study design and analysis were not available. For example, the definition of early menopause was not specified, nor was it clear if the term "passive smokers" included those exposed to a parent or only to a spouse who smoked. Whether the decrease of 2 years in the age at menopause of passive smokers was statistically significant is not discussed. The finding of an association with maternal, but not paternal, smoking during the subject's childhood appears inconsistent. However, the estimate (OR) of the maternal association is based on very small numbers and is probably imprecise. On the other hand, children may be more exposed to their mother's smoking habits than to their father's, and children of mothers who smoke may also have been exposed *in utero*.

Tajtakova *et al.* (1990)

One additional study (Tajtakova *et al.*, 1990) provided data on age at menopause and exposure to ETS, but it was published in Slovak and therefore could not be thoroughly evaluated. According to the English abstract, women who were smokers had a mean age at menopause 1.7 years younger than that of nonsmokers; the dose-response relationship was such that the mean age at menopause was up to 2.4 years earlier in heavier smokers, consistent with other studies. Those exposed to ETS had a mean age at menopause that was slightly younger than nonexposed nonsmokers, but the difference was not statistically significant. We calculated a difference of -0.7 years (95% CI = -1.9 to 0.51) from data presented in a table. These differences are unadjusted for confounders.

5.3.3 Animal Studies of Other Female Reproductive Effects and Tobacco Smoke Exposure

No material was located which used an animal model for menopause.

5.3.4 Discussion and Conclusions

Two studies found indications of early menopause associated with ETS exposure, which is consistent with findings of early menopause among active smokers. The possible mechanisms described in relation to infertility (Section 5.2.4), such as hormone perturbations or oocyte destruction, might also influence age at menopause. The magnitude of the effect of ETS exposure on age at menopause, because it is similar to that of active smoking, seems large in one of the studies. However, studies of the effect in active smokers generally compare smokers to all nonsmokers, including those exposed to ETS. If there is an association with ETS exposure as well, studies of active smokers should exclude ETS-exposed women from the comparison group, which should then strengthen the association seen with active smoking. Everson *et al.* (1986) demonstrated

such a phenomenon in their data. More studies are needed to confirm this finding of decreased age at menopause with exposure to ETS. While human studies have examined the effects of active smoking on menstrual disturbances and hormonal status, none were found that examined these in relation to ETS exposure.

In conclusion, there is a paucity of data on the association of ETS exposure and lowered age at menopause or other measures of menstrual cycle dysfunction, and conclusions regarding causal associations cannot be reached.

5.4 Male Reproductive Toxicity

Male reproductive toxicity includes altered sperm parameters, such as lower density, decreased motility or abnormal morphology, and effects on fertility.

5.4.1 Overview of Human Studies of Male Reproductive Toxicity and Active Smoking

Several studies have shown an association between active smoking and altered sperm parameters, including abnormally shaped sperm (Evans *et al.*, 1981), decreased seminal fluid and decreased sperm motility (Marshburn *et al.*, 1989). Authors of a recent meta-analysis of the literature on sperm density and smoking (Vine *et al.*, 1994) concluded that smokers' sperm density is on average 13-17% lower than that of nonsmokers. The 1980 Surgeon General's Report (U.S. DHHS, 1980) states that "spermatogenesis, sperm morphology, sperm motility and androgen secretion appear to be altered in men who smoke". These outcomes could result from some of the same mechanisms proposed to explain the effects of smoking on female reproductive functions, namely alterations in hormone regulation and gamete production.

5.4.2 Human Studies of Male Reproductive Toxicity and Exposure to ETS

No published studies were found that were designed to examine the association between ETS exposure of males and altered sperm parameters or fertility. The report by Wilcox *et al.* (1989) of their Minnesota study (described above in Section 5.2.2.2) briefly states that childhood ETS or *in utero* exposure of the husband was not related to the couple's fecundability (*i.e.*, time to pregnancy). Another study (Ratcliffe *et al.*, 1992) examined the effects of early exposure to maternal smoking on fertility in adult males using data from clinical trials of diethylstilbesterol treatment (DES). This study could not separate *in utero* exposures (due to maternal active smoking) from postnatal ETS exposure. The authors reported no significant effects on sperm quality, hormone levels or perceived infertility in the sample of 229 men in the follow-up study. However, among the subgroup of men not exposed to DES, there was a significant decrease in sperm motility and a significant increase in oligospermia (deficiency in the number of spermatozoa in the semen); this subgroup is probably more representative of the general population than those who were exposed to DES. Confounders other than adult smoking status of the subjects were not assessed. Compared to nonsmokers, men who smoked as adults had a significantly lower percentage of sperm with normal morphology, after adjustment for maternal smoking and DES exposure.

5.4.3 Animal Studies of Male Reproductive Toxicity and Exposure to Tobacco Smoke

No animal studies specifically examining male fertility and exposure to mainstream or sidestream smoke were located. There are some limited data on testicular pathology from chronic toxicity studies using mainstream smoke. Viczian (1968) reported disruption of the sperm cycle in male rats exposed for 15 minutes 8 times daily for 6 weeks. Dontenwill *et al.* (1973a; 1973b) reported a higher incidence of testicular atrophy in hamsters exposed for 6 to 80 months. This effect occurred only with certain cigarettes and particular daily exposure durations. The functional implications of these results are unclear. No studies of testicular pathology using sidestream smoke were located.

5.4.4 Discussion and Conclusions

No epidemiologic or animal studies were found which investigated the association of ETS exposure and male reproductive parameters. A study which examined the effects of early exposure to maternal smoking (both *in utero* and postnatal ETS exposure) found significant differences in sperm motility and oligosperma in the subgroup of subjects not exposed to DES. Associations have been seen in human studies of active smoking and sperm parameters. Therefore, the findings of sub-fecundability in women exposed to ETS by husbands who smoke may in fact be due to direct effects of active smoking on male reproductive capacity, rather than to the effects of ETS exposure of the women.

In conclusion, due to the paucity of data it is not possible to determine whether there is a causal association between ETS exposure and male reproductive dysfunction.

5.5 Chapter Summary and Conclusions

Though active smoking by women has been found to be associated with decreased fertility in a number of studies, and tobacco smoke appears to be anti-estrogenic, the epidemiologic data on ETS exposure and fertility are not extensive and show mixed results. A well-controlled study in the U.S. found no association of conception delays with spousal smoking habits, contrary to the results of two Scandinavian studies which found slight increases in conception delays but were potentially more biased studies. A recent Dutch study also did not find an association, but included maternal smokers. When ETS exposure is defined as spousal smoking (as in all these studies), any association seen may be due to direct effects of active paternal smoking on male reproductive parameters. Two studies have found an association between ETS exposure during childhood and increased fecundability (in adulthood); a third study did not confirm these findings. All three studies are constrained by lack of information on potential confounders related to childhood ETS exposure. Thus, it is not possible to determine from the conflicting epidemiologic studies conducted to date whether or not ETS exposure is associated with changes in female fertility or fecundability.

One study found a strong association of early menopause with ETS exposure, which is consistent with findings of early menopause among active smokers. Another study reported a slight, non-significant decrease in age at menopause. Because the analytic

methods of these two studies could not be thoroughly evaluated, more studies are needed to confirm this finding. While the effect is biologically plausible, at present there is not firm evidence that ETS exposure lowers the age at menopause or affects other measures of female reproductive dysfunction.

No epidemiologic or animal studies were found which investigated the association of ETS exposure and male reproductive parameters. Associations have been seen in human studies of active smoking and sperm parameters. At present, there is inadequate evidence to draw conclusions regarding the effect of ETS exposure on male reproductive dysfunction.

TABLE 5.1
ETS EXPOSURE AND INFERTILITY OR FECUNDABILITY:
ADULT EXPOSURE

Authors (yr) Location	Design (study size)	Exposure Definition	Results¹	Comments
Tokuhata (1968) United States (Memphis)	Questionnaire to next- of-kin. Case-control study of cancer (n = 2,016)	Husband smoked	Had lowest risk of never having been pregnant. OR:OR = 0.67 (0.46-0.98)	Not adjusted. Crude measure of infertility. Lifetime history.
Baird & Wilcox (1985) United States (Minnesota)	Retrospective interview of pregnant volunteers (n = 678)	Husband smoking	No association with delay to conception after adjustment for active smoking and confounders.	Thorough questions about delay. Not a representative sample (high SES). Data not shown.
Suonio <i>et al.</i> (1990) Finland	Retrospective interview at prenatal care clinics, population-based (n = 2,198)	Husband smoking	Adjusted OROR of delayed conception (6-12 mo): = 1.3 (1.2 -1.4), potentiated by age.	No data on intercourse or contraception. Included smokers.
Olsen (1991) Denmark	Retrospective questionnaire to pregnant women (n = 10,886)	Husband smoking	OR:OR = 1.3 (1.0 -1.8) for ≥20 cigs/day and delay >6 mos. In maternal nonsmokers. OR in smokers:OR = 1.6 (1.3 - 2.1) in smokers.	No data on intercourse. Spouse smoking during pregnancy (vs. before).
Florack <i>et al.</i> (1994) The Netherlands	Interview of women planning pregnancy, follow 12 months (n= 259) Prospective	Partner smoking	FR ¹ : = 2.1 (1.2, 3.5) for 1-10 cigs/day FR: = 1.0 (0.7, 1.6) for >10 cigs/day	Not adjusted. Includes female smokers.

¹ OR -= odds ratio; SES -= socioeconomic status; FR -= fecundability ratio; Fecundability ratio (FR) indicates probability of conception at each cycle. FR >1 indicates improved" fecundability, whereas FR <1 indicates sub-fecundability, when comparing 2 groups.

TABLE 5.2
ETS EXPOSURE AND INFERTILITY OR FECUNDABILITY:
CHILDHOOD EXPOSURE

Authors (yr) Location	Design (study size)	Exposure Definition	Results	Comments
Wilcox <i>et al.</i> (1989) Minnesota	Re-interview women who had pregnancy (n = 631)	Parental smoking (childhood ETS and <i>in-utero</i> exposure) ²	FR ¹ := 1.3 (1.1 -1.6) for 1 or 2 household smokers, 1.6 (1.1 -2.2) for more	Biologic plausibility? <i>In-utero</i> exposure FR = 0.9. Other characteristics of moms not ascertained.
Weinberg <i>et al.</i> (1989) North Carolina	Prospective study after stopping birth control (n = 230)	Childhood exposure to smokers. <i>In-utero</i> exposure ²	FR: = 1.0 crude FR: = 1.6 (1.0, 2.4) if exposed to 2 smokers, adjusted. for <i>in-utero</i> exposure and other variables	Selected group. <i>In-utero</i> exposure FR = 0.5 (0.4, 0.8). Exposure prior to attempt to conceive.
Schwingl (1992) California	Prospective exposure (of mother) and cross-sectional (n = 318)	Childhood exposure	FR: = 1.1 for 1 smoker FR: = 1.2 for 2 smokers (p>0.2)	Exposure from mother herself. Adjusted.
		<i>In-utero</i> exposure ²	FR: = 1.2 (0.9-1.4), no dose-response	No association of FR with active smoking.

¹ Fecundability ratio (FR) indicates probability of conception at each cycle. FR >1 indicates "improved" fecundability, whereas FR <1 indicates sub-fecundability, when comparing 2 groups.

² *In-utero* exposure indicates that the mother of the target participant smoked during her pregnancy.

References

- Baird DD, Wilcox AJ (1985). Cigarette smoking associated with delayed conception. *JAMA* **253**(20):2979-2983.
- Barrett-Connor E (1990). Smoking and endogenous sex hormones in men and women. In: N Wald and J Baron (eds), *Smoking and Hormone-related Disorders*. Oxford University Press, Oxford, pp. 183-196.
- Brown S, Vessey M, Stratton I (1988). The influence of method of contraception and cigarette smoking on menstrual patterns. *Br J Obstet Gynaecol* **95**:905-910.
- Canick JA, Barbieri RL (1990). The effect of smoking on hormone levels *in vivo* and steroid hormone biosynthesis *in vitro*. In: Wald N and Baron J (eds), *Smoking and Hormone-Related Disorders*. Oxford University Press, Oxford, pp 209-216.
- Daling JR, Weiss N, Spadoni L, Moore DE, Voigt L (1986). Cigarette smoking and primary tubal infertility. In: M. Rosenberg (ed), *Smoking and Reproductive Health*. PSG Publishers, Littleton, MA.
- Dontenwill W, Chevalier HJ, Harke HP, Lafrenz U, Reckzeh G, Schneider B (1973a). Investigations on the effects of chronic cigarette-smoke inhalation in Syrian golden hamsters. *J Natl Cancer Inst* **51**:1781-1832.
- Dontenwill W, Chevalier HJ, Harke HP, Lafrenz U, Reckzeh G, Schneider B (1973b). Experimental investigations of the effect of cigarette smoke exposure on testicular function of Syrian golden hamsters. *Toxicology* **1**:309-320.
- Essenberg JM, Fagan L, Malerstein AJ (1951). Chronic poisoning of the ovaries and testes of albino rats and mice by nicotine and cigarette smoke. *W J of S, Obstet Gynecol* **1**:27-32.
- Evans HJ, Fletcher J, Torrance M, Hargreave TB (1981). Sperm abnormalities and cigarette smoking. *Lancet* **1**:627-629.
- Everson RB, Sandler DP, Wilcox AJ, Schreinemachers D, Shore DL, Weinberg C (1986). Effect of passive exposure to smoking on age at natural menopause. *Br Med J* **293**(6550):792.
- Florack EIM, Zielhuis GA, Rolland R (1994). Cigarette smoking, alcohol consumption, and caffeine intake and fecundability. *Prev Med* **23**:175-180.
- Howe G, Westhoff C, Vessey M, Yeates D (1985). Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study. *Br Med J* **290**:1697-1700.
- Leichter J (1989). Growth of fetuses of rats exposed to ethanol and cigarette smoke during gestation. *Growth Dev Aging* **53**:129-134.

MacMahon B, Trichopoulos D, Cole P, Brown J (1982). Cigarette smoking and urinary estrogens. *N Engl J Med* **307**:1062-1065.

Marshburn PB, Sloan CS, Hammond MG (1989). Semen quality and association with coffee drinking, cigarette smoking, and ethanol consumption. *Fertil Steril* **52**:162-165.

Mattison DR, Plowchalk DR, Meadows MJ, Miller MM, Malek A, London S (1989). The effects of smoking on oogenesis, fertilization and implantation. *Semin Reprod Endocrinol* **7**:291-304.

Mays CE, Lingen MW, Sumida MP, Willhite MS (1987). Effects of sidestream smoke on murine reproduction and development. *Am Soc Zool* **27**:134A.

McLean BK, Rubel A, Nikitovitch-Winer MB (1977). The differential effects of exposure to tobacco smoke on the secretion of luteinizing hormone and prolactin in the proestrous rat. *Endocrinology* **100**:1566-1570.

Michnovicz JJ, Herschcopf RJ, Naganuma H, Bradlow HL, Fishman J (1986). Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *N Engl J Med* **315**:1305-1309.

Midgette AS, Baron JA (1990). Cigarette smoking and the risk of natural menopause. *Epidemiology* **1**:474-479.

Olsen J (1991). Cigarette smoking, tea and coffee drinking, and subfecundity. *Am J Epidemiol* **133**(7):734-739.

Rajini P, Last JA, Pinkerton KE, Hendrickx AG, Witschi H (1994). Decreased fetal weights in rats exposed to sidestream cigarette smoke. *Fund Appl Tox* **22**: 200-404.

Ratcliffe JM, Gladen BC, Wilcox AJ, Herbst AL (1992). Does early exposure to maternal smoking affect future fertility in adult males? *Reprod Toxic* **6**: 297-307.

Schwingl PJ (1992). Prenatal smoking exposure in relation to female adult fecundability. 1992 Dissertation. United Microfilms International, Ann Arbor, MI. Also: (1993) *Am J Epidemiol* **139**: 654 (abstract)

Seyler LE Jr, Pomerleau OF, Fertig JB, Hunt D, Parker K (1986). Pituitary hormone response to cigarette smoking. *Pharmacol Biochem Behav* **24**:159-162.

Sloss EM, Frerichs RR (1983). Smoking and menstrual disorders. *Int J Epidemiol* **12**:107-109.

Spira A, Mousan J, Schwartz S (1987). Smoking and fecundity. In: Rosenberg MJ (Ed), *Smoking and Reproductive Health*. PSG Publishing Company, Littleton, MA.

Stillman RJ, Rosenberg Mj, Sachs BP (1986). Smoking and reproduction. *Fertility and Ster* **46(4)**:545-566.

Suonio S, Saarikoski S, Kauhanen O, Metsapelto A, Terho J, Vohlonen I (1990). Smoking does affect fecundity. *Eur J Obstet Gynecol Reprod Biol* **34(1-2)**:89-95.

Tachi N, Aoyama M (1983). Effect of cigarette smoke and carbon monoxide inhalation by gravid rats on the conceptus weight. *Bull Environ Contam Toxicol* **31**:85-92.

Tachi N, Aoyama M (1988a). Effects of cigarette smoke exposure on estrous cycles and mating behavior in female rats. *Bull Environ Contam Toxicol* **40**:584-589.

Tajtakova M, Farkasova E, Klubertova M, *et al.* (1990). The effect of smoking on menopause. *Vnitr Lek* **36(7)**:649-653.

Tokuhata GK (1968). Smoking in relation to infertility and fetal loss. *Arch Environ Hlth* **17**:353-359.

U.S. Department of Health and Human Services (U.S. DHHS, 1980). *The Health Consequences of Smoking for Women: A Report of the Surgeon General*. US Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

Viczian M (1968). The effect of cigarette smoke inhalation in rats. *Experientia* **24**: 511-513.

Vine MF, Margolin BH, Morrison HI, Hulka BS (1994). Cigarette smoking and sperm density: a meta-analysis. *Fert and Sterility* **61(1)**:35-43.

Weinberg CR, Wilcox AJ, Baird DD (1989). Reduced fecundability in women with prenatal exposure to cigarette smoking. *Am J Epidemiol* **129(5)**:1072-1078.

Westhoff CL (1990). The epidemiology of infertility. In: Kiely M (Ed), *Reproductive and Perinatal Epidemiology*. CRC Press, Boca Raton, FL, pp 43-61.

Wilcox AJ, Baird DD, Weinberg CR (1989). Do women with childhood exposure to cigarette smoking have increased fecundability? *Am J Epidemiol* **129(5)**:1079-1083.

Witschi H, Lundgaard SM, Rajini P, Hendrickx AG, Last JA (1994). Effects of exposure to nicotine and to sidestream smoke on pregnancy outcome in rats. *Tox Letters* **71**: 279-286